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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/765,324	12/24/96	KOREN E	GMRF143 CIP2

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EXAMINER	
DUFFY, P	
ART UNIT	**PAPER NUMBER**
1645	23

DATE MAILED: 05/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/765,324	Koren et al
Examiner	**Group Art Unit**
Duffy	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on CPA and amendment of 10-7-99.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Dispositi n of Claims

☒ Claim(s) 21, 22, 35-37, 48-51 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 21, 22, 35-37, 48-51 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Applicati n Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Acti n Summary

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 10-7-99 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/765,324 is acceptable and a CPA has been established. An action on the CPA follows.

2. The amendment filed 8-26-99 has been entered into the record. It is noted that the submitted claims 43-46 have been renumbered as 48-51 pursuant to Rule 126 because claim numbers 43-48 already existed in the prosecution history of this application.

Claims 21, 22, 35-37 and 48-51 are pending. Claims 15, 16, 18, 20, 23, 25, 27-30, 41 and 42 having been canceled.

Priority

3. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be updated in this application. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Double Patenting

4. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*,

151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

5. Claims 20, 21 and 35-37 are rejected under 35 U.S.C. 101 as claiming the same invention as that the claim 48, 50 and 51of allowed but not yet issued Application No. 08/268,809.

Specification

6. The title and abstract of the invention is not descriptive of the claimed inventions. A new title and abstract are required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112

7. Claims 48-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants point to page 27, lines 5-16 which describes a method of making an anti-LDL *monoclonal* antibody whose binding to LDL is not dependent on variations of LDL composition and/or conformation wherein *mice were immunized with soluble apoB-100 which had been delipidized, reduced, carboxymethylated and purified by electrophoresis.* This passage does not

provide conception and written description support that which is broadly claimed (i.e. by immunizing with lipoproteins so treated and does not provide support for an immunogen in absence of carboxymethylation, nor does it provide for polyclonal antibodies with the same property. This passage provides for conception of making a monoclonal antibody (not broadly monoclonal and polyclonal) which binds a specific lipoprotein (LDL) by immunization with soluble apoB-100 which had been delipidized, reduced, carboxymethylated and purified by electrophoresis is provided, but nothing more. This written description does not support general conception of making antibodies using lipoproteins which have been delipidized, reduced and generically purified, nor does such logically flow from the specification as originally filed.

Applicants' are required to cancel the new matter in response to this office action. Applicants are reminded that new matter is a written description issue.

8. Claims 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a monoclonal antibody which specifically binds a stable, conformationally independent epitope which is uninfluenced by the lipid content of an apolipoprotein and lipoprotein, comprising: (a) immunizing an animal with a delipidized, soluble, reduced, carboxymethylated and electrophoretically purified apolipoprotein; (b) producing hybridomas from a spleen isolated from the immunized animal; and (c) screening for a monoclonal antibody which specifically binds a stable, conformationally independent epitope which is uninfluenced by the lipid content of an apolipoprotein and lipoprotein, it does not reasonably provide enablement for generically antibodies (i.e. polyclonal and monoclonal) or immunizing with an lipoprotein which has been delipidated, reduced, solubilized and purified. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The claims are drawn to a method of making an antibody with specific properties comprising a single step claim, immunizing. The specification is not enabled for making polyclonal antibodies with the instantly claimed properties because, the polyclonal antibodies would bind across the entire immunogen and not be limited to those with the claimed properties, therefore the claims must include some isolation or purification step. However, in the instant case the specification provides no guidance as to how to purify or isolate polyclonal antibodies with the specifically claimed properties. The specification fails to teach how to predictably and reproducibly make polyclonal antibodies to lipoproteins or aoplipoproteins with the instantly claimed binding properties. The art specifically teaches that the production of polyclonal antiserum is variable and not readily reproducible. Campbell et al (page 3, column 2) teach that

> "Polyclonal antiserum consists of a wide variety of antibody molecules of different specificity and affinity (Fig. 1.1). Each time an animal is bled, it yields a different 'cocktail' of such antibodies as its immune response to the injected and environmental antigen alters and B cell clones emerge and recede. The same animal can yield a highly specific antiserum directed against the chosen antigen in one bleed and a poor antiserum in another . The animal also has a limited lifespan and prior to the days of Mab technology, the death of a single rabbit could cause major problems is a diagnostic laboratory.
>
> There is an additional inter-animal variability among animals which cannot readily be inbred in the same way as small rodents can be inbred to yield pure strains with matching histocompatibility antigens (Section 3.4). While large 'outbred' animals such a s rabbits, sheep and goats, can yield a large quantity of specific antibody, their response to antigen is variable and it was often necessary to immunise up to 30 animals to obtain a high-affinity antiserum."

The specification also fails to teach how to make an immunogen comprising a lipoprotein which has been delipidated, reduced, solubilized and purified. One can not use in a method of making an antibody, that which has not been adequately described in the specification as to how to make.

It would therefore require undue experimentation on the part of the skilled artisan to make polyclonal antibodies, or make antibodies using lipoproteins which has been delipidated,

reduced, solubilized and purified with the instantly claimed binding specificity absent further guidance from applicants.

9. Claims 20, 21 and 48- 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 and 21 are confusing since they depend from canceled claim 18. Correction is required,

As to claims 48, 49, and 51, the claims are confusing because delipidated lipoprotein are no longer lipoproteins per se and thus it is unclear what composition is administered, what is purified from the delipidated, reduced, solubilized lipoprotein. Or is the lipoprotein first purified, then delipidated and reduced ? Is not a lipoprotein already soluble in plasma ? The passage which applicants point to in the specification do not provide guidance as to the metes and bounds of these terms as it applies to lipoproteins. It is unclear how and what is obtained from such. Correction is required.

Claims 48-51 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims are drawn to a method of making an antibody, however the method never achieves the goal of the preamble. The omitted steps are at least: (b) producing hybridomas from a spleen isolated from the immunized animal; and (c) screening for a monoclonal antibody which specifically binds a stable, conformationally independent epitope which is uninfluenced by the lipid content of an apolipoprotein and lipoprotein.

Claim Rejections - 35 USC § 102 or 103

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claim 48 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Guo et al (Journal of Lipid Research, 30:23-38, 1989).

Guo et al teaches immunization of mice with purified apo[a]. Lp(a) which was reduced with DDT and solubilized in a buffer containing DTT and sodium dodecyl sulphate (SDS) (SDS is a known delipidizing agent) (see page 25, column 1, first, second and third full paragraphs). Thus, the immunogen of Guo et al was purified, reduced, soluble and delipidated. Applicants present a single step claim comprising immunizing, the single step is clealry anticipated.

13. Claims 48, 50 and 51 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Zhou et al (Acta Acad Med Hubei, 11(4):298-302, 1990).

The claims are drawn to method of making an antibody comprising the single step of immunizing with a apolipoprotein or lipoprotein which has been delipidated, reduced, solubilized and purified. Zhou et al teach the purification of apolipoprotein A-I (Apo A-I). Apo A-I was precipitated by heparin-citrate buffer (i.e. the instant purified), delipidated with acetone-ethanol (i.e. the instant delipidated), dissolved in Tris-Urea Buffer (i.e. solubilized), subjected to SDS-polyacrylamide gel electrophoresis (i.e. the instant reduction and purification) and elution the gels with SDS-Tris buffer. Zhou et al produces antisera against Apo A-I by immunizing with the delipidated, reduced, solubilized and purified Apo A-I. Since, Apo A-I is present in high density lipoproteins (HDL), antibodies made by purified Apo A-I would also bind lipoproteins which are known to have Apo A-I present. Since Apo A-I is inherently contained in HDL and the specification is unclear as to what the immunogen consists of, the method as it relates to lipoproteins is also deemed anticipated. Applicants present a single step claim comprising immunizing, the single step is anticipated.

14. Claims 48, 49, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al (Acta Acad Med Hubei, 11(4):298-302, 1990) in view of Gooding, J.W., (in Monoclonal Antibodies, Academic Press Inc., Orlando, Florida, 1983, p 56-97).

Zhou et al is set forth *supra*. Zhou et al differs by not making a monoclonal antibody by isolating the spleen from the immunized animal, making hybridomas and screening for binding to the desired apolipoprotein or lipoprotein.

Gooding teaches methods of production of monoclonal antibodies, immunization of an animal (section 3.2), preparation of spleen cells from the immunized animal (section 3.5),

preparation of myeloma cells (section 3.6), fusion protocols to make hybridomas (section 3.8), and screening assays (3.10.2--3.10.10) to screen for antigen binding and subsequent cloning of hybridomas secreting antibodies which bind the antigen of interest.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to make a monoclonal antibody which binds a delipidated, reduced, solubilized and purified Apo A-I, by substituting the Apo A-I immunogen of Zhou et al in the classical methods of Gooding because monoclonal antibodies provide the art recognized advantages of an unlimited supply of an identical detection reagent, reduce interassay variability and increase assay reproducibility.

15. Claims 48, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al (Acta Acad Med Hubei, 11(4):298-302, 1990) in view of Mills et al (in Laboratory Techniques in biochemistry and molecular biology, a guidebook to lipoprotein technique, Elsevier, 1984, pages 384-448)

Zhou et al is set forth *supra*. Zhou et al differs by not delipidated, reduced, solubilized and purifying Apo AII, Apo B, Apo CIII and Apo E.

Mills et al teaches the routine methods of isolation of purified soluble Apo AII, Apo B, Apo CII and Apo E from plasma lipoproteins. Mills et al teach that monospecific antibodies to apolipoproteins are better suited to clinical use for immunoassay determination.

It would have been *prima facie* obvious to one having ordinary skill in the art to isolate Apo AII, Apo B, Apo CII and Apo E from plasma lipoproteins according to Mills et al and further delipidate and reduce the apolipoproteins according to Zhou et al because Zhou et al teach that a purified, solubilized, delipidated and reduced apolipoprotein is suitable as an immunogen to make antibodies. One would have been motivated to make antibodies to Apo AII, Apo B, Apo CII and

Apo E using the immunogen as modified supra because Zhou et al teach that antibodies to Apo AI and Apo B are useful in immunoassays for the differential diagnosis of coronary heart disease and Mills et al teach that apolipoprotein antibodies would be potentially useful and attractive in a clinical setting because the immunoassay is less time consuming.

Status of Claims

16. No claims are allowed. All claims stand rejected.

17. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995.

Patricia A. Duffy, Ph.D.
April 25, 2000

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600